β-Carotene and lung cancer: a case study[1,2]

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ABSTRACT The conflicting evidence of the relation between β-carotene and lung cancer in humans serves as a poignant case study with respect to what types of evidence are sufficient to support or change a nutrition recommendation. This article is a review of the available evidence of the relation between β-carotene and lung cancer, including data regarding β-carotene intake (from diet and supplements), β-carotene biochemical status, and vegetable and fruit consumption, and a discussion of the role of this evidence in making nutrition recommendations. More than 30 case-control and cohort studies were conducted over many years in various populations and indicated that people who eat more vegetables and fruit, foods rich in carotenoids, and carotenoids (β-carotene in particular), as well as those with higher blood β-carotene concentrations, have a lower risk of lung cancer than those who eat fewer such foods or have lower β-carotene concentrations. In contrast, the intervention results from large, controlled trials of β-carotene supplementation do not support the observed beneficial associations or a role for supplemental β-carotene in lung cancer prevention; instead, they provide striking evidence for adverse effects (ie, excess lung cancer incidence and overall mortality) in smokers. The findings require that caution be exercised in recommending supplemental β-carotene, particularly for smokers, and argue against changing the vegetable-fruit recommendations in the direction of greater nutrient specificity. This case study of β-carotene and lung cancer stresses the importance of having results from at least one, and preferably more, large, randomized intervention trial before public health recommendations concerning micronutrient supplementation are considered. *Am J Clin Nutr* 1999;69(suppl):1345S–50S.

KEY WORDS β-Carotene, carotenoids, antioxidants, lung cancer, clinical trials, epidemiology, prevention

INTRODUCTION

The conflicting evidence of the relation between β-carotene and lung cancer in humans serves as a poignant case study with respect to what types of evidence are sufficient to support or change a nutrition recommendation. The beneficial association supported by overwhelming observational epidemiologic data was abruptly challenged by the results of a few controlled trials of β-carotene supplementation. For reasons that will become clear in the course of this article, one of the central aspects of this study is highlighted by acknowledging that it would be less controversial were it titled "Vegetable consumption and lung cancer."

In this article, available evidence concerning the relation between β-carotene and lung cancer is reviewed and evaluated. To this end, relevant studies regarding β-carotene intake (including that from dietary and supplemental sources), β-carotene biochemical status, and vegetable and fruit consumption are taken into account and summarized. Randomized intervention trials are included in the definition of nutritional epidemiology in that they are among the state-of-the-science methods available to and used by chronic-disease epidemiologists to disentangle many of the myriad important diet-health associations under investigation. The term *observational epidemiology* is used to describe case-control and cohort studies.

DIETARY GUIDELINES RELEVANT TO β-CAROTENE INTAKE

Although dietary guidelines relevant to β-carotene intake are not discussed here in detail, they are germane as background to the case of β-carotene and lung cancer. In general, such guidelines lag behind available research and, rightfully, come after consensus building has taken place.

Two decades of dietary guidelines for Americans published jointly by the US Department of Agriculture (USDA) and the Department of Health and Human Services (DHHS) have mirrored the developing body of research concerning diet and health (1). As of 1980 and 1985, respectively, the guidelines pertaining to nutrition and cancer—and relevant to lung cancer and β-carotene in particular (albeit nonspecifically)—were "eat a variety of foods" and "eat foods with adequate starch and fiber." In 1990 "eat a variety of foods" remained a guideline but "choose a diet with plenty of vegetables, fruits, and grain products" replaced the reference to starch and fiber. This no doubt reflected, in part, the growing literature regarding the inverse association between vegetable and fruit consumption and cancer risk. By 1995, grain products were placed ahead of vegetables and fruit in the guidelines, presumably to better reflect the structure of the USDA food pyramid. Other relevant and somewhat more specific recommendations include the 1989 National Research Council *Diet and Health* report supporting consumption of ≥5 fruit and vegetable

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servings/d and the National Cancer Institute–DHHS sponsorship of the 5-A-Day Program initiated in 1991, which similarly promotes ≥5 servings of fruit and vegetables/d (2, 3).

Although there is no recommended dietary allowance for β-carotene, the recommendation for vitamin A of 800 and 1000 retinol equivalents (or μg retinol) for adult women and men, respectively, represents ≈4.8 and 6.0 mg β-carotene intake daily, assuming that the entire vitamin A requirement is met by provitamin A β-carotene. Therefore, current official public health guidelines are food-based and, specifically, oriented toward vegetables and fruit.

β-CAROTENE AND LUNG CANCER: WHAT IS THE EVIDENCE?

Historical overview

Research concerning β-carotene and lung cancer evolved for the most part similarly to that of many other questions of dietary factors and disease, such as the roles of dietary fats and fiber in human health, as follows. *1*) Data from human studies bearing on the issue were accumulated, especially from observational case-control and cohort investigations published in the 1970s and 1980s. These are reviewed in detail below. *2*) Abundant research was conducted on the antineoplastic effects of carotenoids and retinoids (4, 5) and the antioxidant and other biological functions of carotenoids (6). *3*) Scientific discussion and debate was initiated, followed by additional research and published reviews. This occurred in the late 1980s and early 1990s. One early, widely cited paper by Peto et al (7) highlighted the potential public health significance of β-carotene and the need for controlled trials. Tacit calls for some action (ie, soft or unofficial recommendations) in this phase when the available data were highly suggestive and promising and increased scientific activity during this time may have contributed to the rising popularity of vitamin supplements during the 1980s (8, 9). *4*) Randomized intervention trials to address the role of supplementation with specific micronutrients in cancer prevention were begun in the 1980s and some were completed by the mid-1990s. *5*) The entire body of evidence was reinterpreted, with further discussion, debate, and consensus conferences in the mid-1990s.

Observational epidemiologic studies of lung cancer and vegetables, fruit, and β-carotene

For more than a decade, overwhelming observational evidence has existed that supports an association between lower lung cancer risk and greater consumption of carotenoid-rich foods and, specifically, higher β-carotene intake. By most standards this is among the most consistent and convincing associations in the nutritional epidemiologic literature. What follows is a brief summary.

More than 30 case-control or cohort studies of relevance to the β-carotene–lung cancer association were conducted during the past 2 decades using various measures in diverse populations. Several excellent, comprehensive reviews of this research were published, including those by Ziegler (10), Willett (11), Steinmetz and Potter (12), Block et al (13), van Poppel and Goldbohm (14), and Ziegler et al (15). The observational studies link low self-reported consumption of vegetables or fruit (or both), derived from dietary histories or food-frequency or other dietary questionnaires, with increased risk of lung cancer. In many of the investigations, the inverse relation extends to the consumption of carotenoid-rich foods specifically, such as dark-green, yellow, or orange vegetables. Furthermore, in many studies a protective association was shown for β-carotene intake in particular, and several of these related lower lung cancer risk with higher biochemical status (usually serum concentration) of β-carotene. Relative risk increases of between 50% and 150% (ie, a relative risk of 1.5–2.5) were reported typically for the lowest vegetable-fruit or β-carotene categories compared with the highest. Thus, the observed associations are relatively strong and have substantial public health implications. They were shown in studies of men and women (16), in several racial groups (17), and in current smokers, former smokers, and nonsmokers (18) and therefore appear quite generalized. Taken together, these investigations of carotene-rich vegetables, β-carotene intake, and serum or plasma β-carotene concentrations in relation to lung cancer provide perhaps the most persuasive evidence for an association available in the diet-cancer epidemiologic literature today, both with respect to the magnitude and consistency of the protective association.

From the perspective of developing guidelines for the public, it is relevant and instructional to speculate about what nutrition recommendations regarding β-carotene intake might have resulted if they were based solely on the data from this body of observational research. If the β-carotene supplementation trials had not been conducted, for example, it is possible that guidelines more specific than those promoting greater consumption of vegetables and fruit might have emerged. On the basis of criteria such as consistency and strength of association, dose-response gradient, and biological plausibility, the evidence could have been considered sufficient to support additional recommendations concerning either carotenoid-rich foods or β-carotene intake in particular. Furthermore, a nutrient-specific guideline for β-carotene intake need not have specified source. A recommendation for adult daily intake of 10 mg β-carotene, for example, could be satisfied from either dietary or supplemental sources. This intake is only 67% higher than the β-carotene equivalent of the recommended dietary allowance for vitamin A for men and is well within the range of intake reported for the highest categories of β-carotene intake in the observational studies. However, such a recommendation has not been made to date, in part because of the results of the studies described below.

Randomized intervention trials of β-carotene and lung cancer

Randomized intervention trials provide highly relevant, specific, and convincing evidence regarding supplemental nutrients (or dietary patterns) and cancer risk and have an important role in the development of related nutrition recommendations. They test specific nutrients, nutrient combinations, or dietary interventions through randomized experimental designs that avoid most of the biases inherent in observational studies. Two large randomized intervention trials of β-carotene supplementation having lung cancer as the primary study endpoint were published: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study and the Beta Carotene and Retinol Efficacy Trial (CARET) (19, 20). Two other large, randomized cancer intervention trials also reported data concerning the effects of β-carotene supplementation on lung cancer: the Nutrition Intervention Trial conducted in Linxian, China, and the Physicians' Health Study (21–23).

In early 1994 the ATBC Study Group reported its initial trial intervention findings concerning β-carotene and α-tocopherol supplementation (19). This was the first report from a large (> 29 000 participants), double-blind, placebo-controlled trial on the prevention of lung cancer and other cancers by supplementation with micronutrients. The results for β-carotene (20 mg in 1 capsule taken daily for 5–8 y) were surprising in that they provided no evidence for benefit in the prevention of lung cancer in older male cigarette smokers and instead suggested an adverse outcome, with more incident lung cancers diagnosed in those receiving β-carotene supplements. By the end of the study, and as reported in the final report for lung cancer, lung cancer was diagnosed in 482 men in the β-carotene–supplemented group and 412 in the group not receiving β-carotene (24). This represented relative excess of 16% for the β-carotene group. With a 95% CI of a 2–33% increase in lung cancer incidence, the finding was clearly inconsistent with the 2-fold risk reduction attributed to high β-carotene intake in so many observational studies, and it essentially ruled out a primary preventive effect on lung cancer of a 5–8-y regimen of a 20-mg β-carotene supplement in smokers. The significance of this unexpected finding was heightened by the fact that the β-carotene group also experienced increased overall mortality (ie, by 8%), including an apparent increase in ischemic heart disease mortality. The interpretation of more than a decade's worth of research on the relation between β-carotene from vegetables and fruit and lung cancer was suddenly brought into question by these findings.

A similar result for β-carotene was subsequently reported by CARET, which halted its intervention of β-carotene (30 mg) and retinyl palmitate [25 000 IU (13 664 retinol equivalents)] after an observed increase in lung cancer incidence and total mortality in the supplemented group (20). This trial studied >18 000 men and women, of whom 388 developed lung cancer, with a 28% increase in lung cancer incidence in participants who received the β-carotene–retinyl palmitate combination daily for an average of 4 y compared with participants who received placebo. Increased total mortality (17%) was also observed in the supplemented group. Until these CARET results were announced and published in early 1996, the ATBC Study findings were viewed cautiously and, by some, with skepticism. Thereafter, the concordant data from the ATBC Study and CARET created a striking apparent contradiction to the previous observational epidemiology.

Some aspects of design and findings common to both the ATBC Study and CARET are the random assignment of persons at rather high risk for lung cancer because of cigarette smoking, asbestos exposure, or both; the very high serum concentrations of β-carotene achieved; and similar relative risk increases (though somewhat greater in CARET) for lung cancer incidence and total mortality. CARET differed from the ATBC Study in that it tested a β-carotene–vitamin A combination and included women and both current and former smokers as well as a large group of workers exposed to asbestos.

One finding in both trials that has received less attention but is highly significant for the present purposes is that the trial participants with lower baseline β-carotene intake or β-carotene serum concentrations at baseline experienced higher lung cancer incidence during the study, independent of the intervention effects (19, 24, 25). This is consistent with the previously discussed observational epidemiologic studies. In the ATBC Study this was seen in the group not supplemented with β-carotene, with 15% and 33% higher lung cancer incidence rates in subjects in the lowest quartiles of β-carotene intake and serum β-carotene, respectively, compared with those in the highest quartiles (24). Thus, within this one study both the expected beneficial relation between dietary and serum β-carotene status and lung cancer risk and the apparently adverse effect of active supplementation with 20 mg/d were observed. Results from CARET corroborated this finding (25).

The fact that the relative risk estimates for the dietary and serum β-carotene associations are not as large as in many of the prior observational studies could be easily attributed to the greater homogeneity and higher baseline risk of the ATBC Study and CARET populations. The demonstration of these protective associations, along with other established etiologic associations with lung cancer, such as risk increasing with age, number of cigarettes smoked daily, years and pack-years of cigarette smoking, degree of inhalation, and occupational asbestos exposure, added to both the validity and the generalizability of the studies' findings. It also brought to bear the question of how and why the apparently contradictory results occurred (discussed below).

In contrast with the findings from the ATBC Study and CARET, the Physicians' Health Study of 22 000 male, primarily nonsmoking physicians in the United States showed no effective difference in lung cancer incidence after 12 y of supplementation between the β-carotene group (50 mg on alternate days) and placebo group (23). This was based, however, on only 66 and 71 cases in the 2 groups, respectively, and represented a nonsignificant 7% reduction. No adverse or beneficial effects were observed in the β-carotene group, even in the small number of smoking participants (11%).

Nutrition intervention trials in the general population of Linxian, China, investigated the effects of selected micronutrients on the incidence of esophageal cancer and total mortality in nearly 30 000 men and women (primarily nonsmokers) (21). This is the only large population trial to have shown preventive effects (ie, for stomach cancer and total mortality) of a combined supplement of β-carotene, α-tocopherol, and selenium. As subsequently reported (22), there were only 31 lung cancer deaths among the 792 total cancer deaths, with slightly fewer in the group that received the supplemental β-carotene combination (11 compared with 20 deaths). Because of the nature of the combination micronutrient supplement, intervention effects from this trial could not be attributed to any 1 of the 3 agents with certainty.

In total, these trials provide solid evidence for a relatively small adverse effect of β-carotene supplementation on lung cancer in cigarette smokers. For the purposes of the present discussion, it is important to note that such an effect was detectable because of the large size and controlled experimental design of these studies, which minimized or eliminated confounding factors. Had these studies not been conducted, the observational research would likely have continued to be interpreted in favor of β-carotene being the sole beneficial substance, and the potential downside for higher-dose supplementation may never have been observed or considered possible. Investigation of the trial findings is currently underway globally and will likely lead to a greater understanding of both the role of carotenoids in human health and of carcinogenesis itself.

Although discussion of the possible biological mechanisms behind the observed adverse effects of supplemental β-carotene is beyond the scope of this article, insofar as they have potential relevance to any recommendations regarding β-carotene they are mentioned briefly. One issue in need of further investigation is whether such effects are limited to high-risk groups such as current smokers. For example, if it is corroborated through laboratory studies that such toxicity resulted from combining a high-dose β-carotene supplement with active cigarette smoking through a direct interaction between cigarette smoke and β-carotene in lung tissue, as has been discussed (26), this might suggest particular caution regarding β-carotene use by cigarette smokers. A similar logic could be used if the findings were explained by the combination of β-carotene and heavy alcohol consumption (24, 27). If the effect were dose related, then lower dosages might be considered for further study in certain populations. However, the striking lack of benefit in the Physicians' Health Study, with its primarily nonsmoking population and blood β-carotene concentrations less than half that of the ATBC Study or CARET, argues against a likely benefit in nonsmokers or from lower dosages.

INTERPRETATION OF CONTRADICTORY STUDY RESULTS AND IMPLICATIONS FOR RECOMMENDATIONS

Results from observational studies have indicated clearly that persons who report eating more vegetables and fruit, more foods rich in carotenoids, and more carotenoids and β-carotene in particular are less likely to develop lung cancer than those who eat fewer vegetables and fruit and less β-carotene. Some studies also showed that persons with higher blood β-carotene concentrations are at reduced risk for lung cancer compared with those with lower concentrations (14, 15). Recent data from some of the trials corroborate this by showing that regardless of their intervention assignment, study participants with higher intake and serum concentrations of β-carotene at baseline developed fewer subsequent lung cancers (24, 25).

From the standpoints of consistency in the literature, risk level, dose-response gradient, and temporal correctness, the reported observational associations with lung cancer are no doubt real. Indeed, the only plausible way the associations might not be real is if vegetable, fruit, and β-carotene intakes were strongly related to another truly protective (and unmeasured) exposure that is confounding their association with lung cancer; however, no such factor has yet been identified. Although some studies lacked sufficient control or adjustment for known potential confounding factors, such as smoking history, most involved adequate control.

The similarity of the associations for vegetables and fruit and β-carotene (and possibly other carotenoid) intake have been interpreted as being consistent with specific beneficial effects of this substance, the biological plausibility of which is supported by studies of several properties and functions of β-carotene, for example, antioxidation, inhibition of tumor initiation and promotion, and enhancement of immunity and cellular maturation. However, similar supportive functional research is also available for other substances found in vegetables and fruit, for example, folic acid (28) and ascorbic acid (29). Therefore, on the basis of this body of observational evidence, nutrition recommendations promoting vegetable and fruit consumption are warranted. This is strengthened by the fact that beneficial associations have also been recognized between such diets and other major chronic diseases, notably heart disease (30–33).

The trial intervention results, however, do not support the observed associations or a role for supplemental β-carotene in lung cancer prevention in the populations, dosages, and duration of supplementation tested, and they are, on the surface, at odds with the observational epidemiology. Taken together, the 4 large β-carotene trials having experimental data for >1400 lung cancer cases, and particularly the ATBC Study and the CARET, representing ≈1300 cases between them, make it highly unlikely that pharmacologic doses of supplemental β-carotene are beneficial in the prevention of most lung cancers and provide strong evidence for adverse effects (eg, increased tumor promotion or progression) in smokers. These studies raise the issue of interpretation of the cohort and case-control studies (eg, is it the β-carotene in the diet?) and have reopened the issue of the safety of β-carotene supplements, which had long been considered a nonissue. Their results require that some caution be exercised in recommendations concerning supplemental β-carotene and argue against changing related dietary recommendations in the direction of greater nutrient specificity at this time.

Additional research holds the key to providing us with a more complete understanding of these etiologic relations. In a sense, the trial results have by necessity returned the focus to observational epidemiologic studies and basic research. Observational epidemiology should again revisit carotenoids, foods, and related biochemical factors. Specifically, further evaluation of other carotenoids and phytochemicals, both in the diet and in serum, is clearly warranted because any one or more of these substances present in vegetables and fruit might be responsible for the inverse association with lung cancer. Initial studies of this kind include those of Le Marchand et al (34) and Ziegler et al (35), which further explored the role of other dietary carotenoids using newly available food-composition data. These studies identify protective associations not only for β-carotene, but for α-carotene and lutein, for example, while showing stronger relations for vegetable consumption per se. They also show that disentangling the component effects of the highly collinear dietary carotenoids is both challenging and possible.

Other investigations should further explore the issue of vegetable and fruit consumption compared with β-carotene and carotenoid intake or serology (or, where possible, both intake and serology) and evaluate associations for dietary and supplementary sources of the micronutrients. Depending on results from additional studies such as these, further testing of supplemental β-carotene (at lower dosages in lower-risk groups), other carotenoids, or other phytochemicals may be warranted once concerns about safety have been addressed. The testing of multiple nutrients, either as combinations or in factorials designs, affords the opportunity of looking at biologically based interactions and yields more information per study.

One other important issue must be considered. Any recommendation for or related to β-carotene—or for that matter any nutrient—must consider the potential effects on all important health outcomes. Each large supplementation trial has typically reported its intervention findings for most important events, such as cancer, cardiovascular disease, and total mortality. In this way, overall efficacy of β-carotene supplementation is evaluable. Although most observational (especially case-control) studies are endpoint specific, reference to the association between β-carotene and other important endpoints is also possible in cohort studies. For example, the Western Electric Study reported an inverse association between dietary carotene index and lung cancer mortality, especially in heavy smokers (36). A recent report from the study showed a similar inverse association between the carotene index and cardiovascular and overall mortality (37). Through more complete data such as these, the beneficial association between β-carotene and lung cancer can be weighed along with evidence regarding its effects on other outcomes, with more informed recommendations resulting.

CONCLUSIONS

The quantity and quality of the relevant studies, the degree of consistency among the data, the availability of a plausible mechanism or set of mechanisms, and, importantly, the beneficial (or lack of adverse) effect on other aspects of human health and disease are all highly relevant to the issue of nutrition recommendations. The case study of β-carotene and lung cancer strongly supports—if not mandates—the need for results from at least one, and preferably more, large, randomized intervention trial before the consideration of public health recommendations concerning micronutrient supplementation. Overwhelming and highly consistent observational data in favor of a beneficial association for β-carotene and carotenoids, although truly impressive, did not provide the entire picture. In the case of β-carotene and lung cancer, the trial results raised further questions that require the testing of specific hypotheses.

The β-carotene–lung cancer association is sufficient to affect recommendations only insofar as they support current guidelines concerning enhanced vegetable and fruit consumption. It is clear that persons who eat a relatively large quantity of vegetables and fruit have a substantially lower risk of developing lung cancer (12, 13), and they may experience less cardiovascular disease and delayed mortality as well. Although many available studies (14, 15) strongly implicate β-carotene and possibly other carotenoids as among the putative agents of benefit, certainty around this issue is lacking. Protective associations for greater consumption of vegetables and fruit have often been stronger than those for β-carotene (or total carotenoid) intake specifically, suggesting the possibility of an etiologic relation with lung cancer for something in such diets beyond one or a few of the micronutrients—that is, the whole being greater than the sum of its parts. Further, the supplementation trials suggest not only lack of benefit of β-carotene in lung cancer prevention, but possible harm in smokers from not only lung cancer but overall mortality as well.

Before changes are made to the current guidelines regarding foods, vegetables, and fruit, more definitive evidence is needed about specific micronutrients such as β-carotene. It is likely that neither the public nor the scientific community will be satisfied with recommendations concerned solely with foods and will remain curious about what in foods is responsible for the consistent protective association observed for cancer.

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